REMARKS/ARGUMENTS

I. Introduction

Claims 10-25, 27, 32-34, 66-68, and 70 are pending in this application. Claims 1-9, 16-24, 26, 28-31, 35-65, and 69 have been canceled. Claims 10-15, 25, 27, 33, 34, 66, 67, 68, and 70 have been amended to correct informalities. Claim 10 has been amended to recite "A mutant *ras* peptide comprising: an amino acid sequence of at least 8 to no more than 13 amino acids, wherein said amino acid sequence comprises . . . ." This amendment has support at p. 10, lines 1-2 of WO 97/40156 Al. Claim 10 has also been amended to recite " ... or serine" in order to agree with the description of the sequence listing filed July 21, 2000 (bottom of p. 5). Applicants have changed claim 14 to recite "wherein Xaa_2 is selected..." in order to correct a typographical error and to correctly reflect original claim 14. Claim 71 has been added to recite a previously deleted dependent claim. No new matter has been added in the amendments. Reconsideration and allowance of the pending claims is earnestly requested.

Applicants thank the Examiner for withdrawing the previous rejection under 35 U.S.C. § 112, second paragraph and the objection to the specification set forth in Paper No. 35.

II. Rejections Under 35 U.S.C. § 103(a)

A. Claims 10-15, 27, and 32

The Examiner has maintained the rejection of claims 10-15, 27, and 32 under 35 U.S.C. § 103(a) as set forth in Paper Nos. 16, 23, and 35. The Examiner has rejected the claims under 35 USC § 103(a) as being unpatentable over Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or U.S. Patent No. 5,861,372 ("the '372 patent"). Van Elsas *et al.* and Gjertsen *et al.* allegedly teach the claimed peptide and differ only by the absence of an N-terminus tyrosine. Ruppert *et*

al. and the '372 patent allegedly provide two separate reasons for modifying the peptides of the primary references by the inclusion of an N-terminus tyrosine.

Applicants respectfully traverse the Examiner's rejection that the peptide of the claimed invention is obvious in view of Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, or the '372 patent. Applicants again remind the Examiner that M.P.E.P. § 2142 sets forth three requirements that must be met in order to establish a *prima facie* case of obviousness under § 103. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references. Second, there must be a reasonable expectation of success upon combining such references. Finally, the prior art references, when combined, must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L. Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* M.P.E.P. §§ 2142-43 (February 2003). Thus, the Examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs, or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an Examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for

example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants submit that the rejections do not meet this test.

1. Van Elsas *et al.* in view of Ruppert *et al.* or the '372 Patent

Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to successfully substitute the claimed N-terminus K of Van Elsas *et al.* with an N-terminus Y as allegedly taught by Ruppert *et al.* in order to facilitate either better binding of HLA-A2, as allegedly taught by Ruppert *et al.* or to facilitate the addition of detectable labels to peptide fragments as allegedly taught by the '372 patent. Nor do the combined references teach all of the limitations of the claimed invention.

Van Elsas *et al.* teach the *in vitro* stimulation of lymphocytes derived from a healthy donor. Van Elsas *et al.* also teach 9 and 11 mer peptides derived from normal and mutant *ras* sequences that are able to bind HLA-A*0201 and are subsequently used to induce CTL reactions in peripheral blood mononuclear cells from normal donors. Van Elsas *et al.* teach that the 9 and 11 mer peptides "strongly bind" to HLA class I molecules (p. 393, left col.). Because the 9 and 11 mer peptides taught in Van Elsas *et al.* already strongly bind to HLA class I molecules, one of ordinary skill in the art would not likely be motivated to improve binding by choosing Y from the potential residues that are "associated with good binding" (p. 932, Figure 3) taught by Ruppert *et al.*, as a substitute for K on the N-terminus of the peptide sequence KLVVVGADGV taught in Van Elsas *et al.*

The Examiner has asserted that because the peptide taught in Van Elsas *et al.* binds human MHC HLA-A, such peptide would be inherently capable of "eliciting" a lymphocyte,

which the Examiner has extrapolated to mean "eliciting a $CD8^+$ response". Van Elsas *et al.* teach *activation* of "naive $CD8^+$ cytotoxic T lymphocytes" (p. 389, left col.) and do not teach *eliciting* a $CD8^+$ response. Activation of naive CTL is not clearly the same as *ras* peptides eliciting a "peptide-specific human $CD8^+$ cytotoxic T lymphocyte *immune response*" (emphasis added), as in the claimed invention. "Activation" of CTL means the stimulation of CTL by specific antigen or nonspecific mitogens resulting in macromolecular synthesis (RNA, protein, and DNA) and production of lymphokines, followed by proliferation and differentiation of the progeny into various effector and memory cells. "Eliciting" CTL means to obtain, produce, or bring forth CTL. Furthermore, although Van Elsas *et al.* teach the induction by p21ras peptides of "CTL reactions" (p. 389, right col.), Van Elsas *et al.* do not specifically teach that these reactions elicit a peptide-specific human $CD8^+$ CTL immune response.

Ruppert *et al.* teach a structural study of residues in peptide binding and do not teach or suggest that it would be desirable to use a peptide with a Y on its N-terminus end in studies of *in vitro* stimulation of CTL.

Applicants respectfully submit that there would also have been no motivation to combine Van Elsas *et al.* with the '372 patent. The Examiner has stated that it would have been obvious to substitute Y (i.e., lysine or tyrosine) at the N-terminus end of the peptide taught by Van Elsas *et al.* to facilitate the addition of detectable labels to said fragments, as taught in the '372 patent. The '372 patent teaches an angiostatin or angiostatin-derived peptide sequence, and briefly teaches at col. 22, lines 25-28, the possibility that "tyrosine or lysine ... [can be] added to fragments that do not have these residues to facilitate labeling of reactive amino and hydroxyl groups on the peptide." Applicants point out, however, that Van Elsas *et al.* already teach at p. 390, right col., a method of identification of the amino acid sequences that bind HLA-A*0201,

wherein "target cells were radiolabeled with sodium-chromate", "incubated with peptide", and "added to the CTL". Thereafter, "[b]locking studies were done by incubation for 30 min with antibodies, after labeling and peptide pulsing." If the peptide sequences of Van Elsas *et al.* already bind strongly to HLA class I molecules, as mentioned above, and Van Elsas *et al.* already teach a satisfactory method of labeling, it is unclear why one of ordinary skill in the art would be motivated to seek out another labeling method, such as that taught in the '372 patent.

Thus, Van Elsas *et al.* in view of Ruppert *et al.* or the '372 patent do not teach all of the limitations of the claimed invention, and one of ordinary skill in the art would not have been motivated to successfully combine Van Elsas *et al.* with Ruppert *et al.* or the '372 patent.

2. Gjertsen *et al.* in view of Ruppert *et al.* or the '372 patent

Gjertsen *et al.* is directed to the results of a phase I/II study of an *ex vivo ras* peptide vaccination in five patients with advanced pancreatic cancer. Gjertsen *et al.* teach a peptide sequence of 17 amino acids that binds MHC HLA-A and elicits $CD8^+$ lymphocytes. Gjertsen *et al.* do not clearly teach a peptide sequence of "about 10 or 13 amino acids", as the Examiner alleges. Nevertheless, without acquiescing in the Examiner's rejection, Applicants have rendered moot the Examiner's rejection of claim 10 in view of Gjertsen *et al.* by amending claim 10 as shown above in the claim amendments to recite "A mutant *ras* peptide comprising an amino acid sequence of at least 8 to no more than 13 amino acids, wherein said amino acid sequence comprises . . . ."

Applicants respectfully submit that as a result of this amendment, the peptides of the instant invention are over 23% smaller than the peptides disclosed by Gjertsen *et al.* Thus, one of ordinary skill in the art would not have been motivated to rely on Gjertsen *et al.* in producing

the peptide of the claimed invention because the peptides are of different sizes. This amendment should also overcome the Examiner's argument that claim 10, as previously amended, provides no limitation to the size of the peptides of the instant claims except a minimum length of 8 amino acids because the claim includes two open modifiers, i.e., "peptide having a size of 8 to 13 amino acids, comprising ...".

Furthermore, the claimed invention is unique over the prior art because the claimed invention provides a human HLA-A2-restricted $CD8^+$ CTL epitope reflecting the codon 12 mutation, Gly to Asp (p. 13, lines 25-26) and the identification of human HLA-A2 restricted, $CD8^+$ CTL epitopes reflecting two distinct codon mutations, which were found to be nested within the longer 13-mer peptide immunogen (i.e., *ras* 5-14 (D12)) (p. 14, lines 13-16).

Applicants respectfully disagree with the Examiner's assertion that Applicants have deemed the results of the Gjertsen *et al.* study insignificant and that Gjertsen *et al.* teach a response rate of 100%, i.e., *all* of the patients experienced at least some relief. Applicants reiterate that Gjertsen *et al.* provide no incentive to the skilled artisan to rely upon the techniques taught in Gjertsen *et al.* because although Gjertsen *et al.* provide a number of 17 mer peptides (p. 451, Table I), Gjertsen *et al.* were not able to make any conclusions other than that *ras* peptide vaccination is safe and *may* result in a potentially beneficial immune response.

Applicants note that despite inconclusive results being due to the "small number of patients treated" (p. 452, right col.), one of ordinary skill in the art would not have been motivated to rely on the techniques in Gjertsen *et al.* because fewer than all 5 of the patients in the study exhibited a concrete *immune response* to the vaccine therapy. A "proliferative T cell response was found in only 2 of the 5 patients vaccinated" (p. 451, right col.; p. 452, Table IV). While Applicants acknowledge that 3 patients "noticed pain relief" (p. 451, right col.), Gjertsen

et al. do not specify whether this pain relief was due to an immune response, but instead refer to these patients as "non-responding" (p. 451, right col.) in contrast to the two "responding" patients in the study who showed an *immune response.*

Furthermore, Applicants respectfully disagree with and find irrelevant to this § 103 rejection the Examiner's argument that the *in vitro* T cell proliferative data in support of the instant invention is not scientifically significant or enabling. Applicants remind the Examiner that a teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the Applicants' disclosure, as Applicants have pointed out above. One of ordinary skill in the art would not have been motivated to rely on the techniques or conclusions in Gjertsen *et al.* or to combine Gjertsen *et al.* with Ruppert *et al.* or the '372 patent because the results in Gjertsen *et al.* were inconclusory, and Gjertsen *et al.* do not teach peptides that are the same size of the instant invention, as described above and per currently amended claim 10. Thus, any combination of Gjertsen *et al.* with either Ruppert *et al.* or the '372 patent would not have made the instant invention obvious.

B. Claims 25 and 66-67

The Examiner has maintained the rejection of claims 25 and 66-67 under 35 U.S.C. § 103(a) as being unpatentable over Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or U.S. Patent No. 5,861,372 as applied to claims 10-15, 27, and 32 above, and further in view of U.S. Patent No. 6,039,948 ("the '948 patent"), for the reasons of record set forth in Paper Nos. 16, 23, and 35.

The Examiner argued in Paper No. 16 that Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, and the '372 patent differ from the claimed invention in that they do not teach a mutant *ras* peptide conjugate comprising said peptide and tetanus toxoid. The Examiner asserted that the

'948 patent teaches a tetanus toxoid-peptide conjugate, used as an adjuvant to elicit an improved immune response when compared to the peptide alone. The Examiner asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made a mutant *ras* peptide-tetanus toxoid conjugate as an immunogen to elicit an improved response when compared to a peptide alone, as taught by the '948 patent, in combination with Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, and the '372 patent.

Applicants respectfully traverse this rejection and rely on the arguments mentioned above for claims 10-15, 27, and 32. Applicants further submit that the '948 patent does not rectify the deficiencies of Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or the '372 patent. One of ordinary skill in the art would not have been motivated to combine the modified tetanus-toxoid-coupled technique of the '948 patent with Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, or the '372 patent. The '948 patent teaches a method for treatment of antigenically modified polypeptides. The '948 patent differs from the claimed invention in that it does not teach a mutant *ras* peptide, eliciting a $CD8^+$ human peptide-specific immune response, or a peptide no less than 8 and no more than 13 amino acids, as in the claimed invention. The '948 patent also primarily teaches eliciting an antibody response in *animals* such as baboons, rabbits, mice, or rats, using a modified hormone peptide to control fertility (col. 9, lines 13-16). All of the tetanus-toxoid conjugated peptide data in the '948 patent involves animals. Van Elsas *et al.* and Gjertsen *et al.* rely primarily upon human, not animal, studies in support of their conclusions.

The peptide sequence of the '948 patent is much larger than those taught in Van Elsas *et al.*, Gjertsen *et al.*, or the '372 patent. The '948 patent states that "the polypeptide modified by the techniques of the instant invention is preferably a fragment of the target protein rather than the intact protein." (at col. 13, lines 53-55), and "it is desirable to use a fragment corresponding

to a portion of the 111-145 [35 amino acid] sequence of the beta subunit ..." (col. 17, lines 46-48). Thus, any combination of Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or the '372 patent and further in view of the '948 patent would not make the invention obvious.

C. Claims 33, 68, and 70

The Examiner has maintained the rejection of claims 33, 68, and 70 under 35 U.S.C. § 103(a) as being unpatentable over Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or U.S. Patent No, 5,861,372 ("the '372 patent") as applied to claims 10-15, 27, and 32 above, and further in view of U.S. Patent No. 5,800,810 ("the '810 patent"), for the reasons of record set forth in Papers No. 16, 23, and 35.

The Examiner has asserted that Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, and the '372 patent differ from the claimed invention in that they do not teach a mutant *ras* peptide composition further comprising said peptide and interleukin 2 (IL-2). The Examiner has alleged that it would have been obvious to one of ordinary skill in the art to have made a mutant *ras* IL-2 pharmaceutical composition in order to elicit an enhanced immune response when compared to an immunogen alone, as taught by the '810 patent, in combination with Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, and the '372 patent.

Applicants respectfully traverse this rejection and rely on the arguments mentioned above for claims 10-15, 27, and 32. Applicants further point out that the '810 patent does not rectify the deficiencies of Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, or the '372 patent. One of ordinary skill in the art would not have been motivated to combine Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, or the '372 patent with the '810 patent. The '810 patent does not rely on human data in support of its conclusions and does not teach a peptide-specific $CD8^+$ human immune response. Rather, the '810 patent relies on animal data, such as pigs, dogs, and mice to support

its conclusions. Van Elsas *et al.* and Gjertsen *et al.* primarily rely on human experimental data in support of their conclusions.

The '810 patent teaches that "whether or not a particular adjuvant preparation will be sufficiently effective in a given instance is not predictable." (col. 1, lines 44-47). Because of the unpredictability in the art of administering a pharmaceutical composition comprising an adjuvant such as IL-2, as taught in the '810 patent to a human subject, as taught in Van Elsas *et al.* or Gjertsen *et al.*, one of ordinary skill in the art would not have been motivated to combine Van Elsas *et al.*, Gjertsen *et al.*, Ruppert *et al.*, or the '372 patent with the '810 patent.

D. Claim 34

The Examiner has rejected claim 34 under 35 § U.S.C. 103(a) as being unpatentable over Van Elsas *et al.* or Gjertsen *et al.* in view of Ruppert *et al.* or U.S. Patent No. 5,861,372 ("the '372 patent") as applied to claims 10-15, 27, and 32-33 above, and further in view of U.S. Patent No. 6,001,349 ("the '349 patent"), for the reasons of record set forth in Papers No. 16, 23, and 35.

Applicants respectfully traverse this rejection and rely on the arguments mentioned above for claims 10-15, 27, and 32-33. Applicants further submit that the Examiner's rejection of claim 34 has been rendered moot by Applicants' amendments to claim 34 filed April 9, 2002 and February 26, 2003, respectively, wherein Applicants deleted the phrase "RIBI Detox™".

Applicants submit that the above identified combinations of references are nowhere supported by the references or in the common knowledge of the art. In *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998), the Federal Circuit stated that "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations . . . mostly of old

elements"). Therefore an Examiner may often find every element of a claimed invention in the prior art just as we could likely find every word in a dictionary. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an Examiner to use the claimed invention itself as a blueprint to defeat the patentability of the claimed invention. Such an approach would be an "illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).

To prevent the use of hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires the Examiner to show motivation to combine the references that create the case of obviousness. In other words, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventors and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants submit that the above-mentioned rejections do not satisfy the strictures of the *Rouffet* decision. The primary references are not combinable without proscribed hindsight. The secondary references do not rectify the deficient and contradictory teachings of the primary references, and therefore the obviousness rejection should be withdrawn.

III. Rejections Under 35 U.S.C. § 112, first paragraph - Enablement

The Examiner has maintained the previous rejection of claims 10-15, 25, 27, 32-34, 66-68, and 70 under 35 U.S.C. § 112, first paragraph, because the specification, while allegedly

being enabling for a mutant *ras* peptide consisting of the sequence YLVVVGADGV, does not reasonably provide enablement for a mutant *ras* peptide comprising (or having) the sequence YLVVVGADGV, for the reasons of record set forth in Paper No. 35. The Examiner has asserted that the phrase "peptide having a size of 8 to 13 amino acids, comprising," which includes two open modifiers (having and comprising) provides no limitation to the size of the peptides of the instant claims except a minimum size of 8 amino acids.

Applicants respectfully traverse this rejection, and without acquiescing in this rejection, Applicants submit that this rejection has been rendered moot by Applicants' amendment of claim 10 as noted above.

IV. Rejections Under 35 U.S.C. § 112, first paragraph - Written Description

The Examiner has introduced a new rejection of claims 10-15, 25, 27, 32-34, 66-68, and 70 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The Examiner has alleged that the specification and the claims as originally filed do not provide support for the invention as now claimed, specifically: "A mutant *ras* peptide having a size of 8 to 13 amino acids". The Examiner has asserted that the specification discloses only a peptide "between about 8 to 13 amino acids", which is not the same as "having a size of 8 to 13 amino acids".

Applicants respectfully traverse this rejection, and without acquiescing in the rejection, Applicants note that this rejection has been rendered moot by the amendment of claim 10, as noted above.

V. Rejections Under 35 U.S.C. § 112, first paragraph - Indefiniteness

The Examiner has newly rejected claims 10-15, 25, 27, 32-34, 66-68, and 70 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner has alleged that the recitation of a peptide having a size of 8-13 amino acids comprising SEQ ID NO:14 encompasses nonsensical embodiments as it would be impossible to have 8 or 9 amino acid peptides comprising 10 amino acid SEQ ID NO:14.

Applicants respectfully traverse this rejection. Applicants note that it is permissible for a numerical value in a dependent claim to be narrower than a previously recited numerical range, as long as the dependent numerical value falls within the range that it is dependent upon, and such range has support in the specification. M.P.E.P. § 2163.05 (*citing In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)). In *In re Wertheim*, the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." The Federal Circuit held that a limitation of "between 35% and 60%" was acceptable. Thus, Applicants submit that a sequence of 10 amino acids is within the range of 8-13 amino acids, as recited in amended claim 10.

VI. Conclusion

In view of the foregoing remarks and amendments, reconsideration of the application and allowance of the claims are respectfully requested. If any issues remain which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at 202-912-2777.

Respectfully submitted,

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Date

John Isacson
Attorney for Applicant
Reg. No.: 33,715

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

Customer No. 26633